

REMARKS

The present invention relates to a protein belonging to the TNF superfamily member membrane bound protein designated TNF-Related Activation Induced Cytokine termed "TRANCE" and nucleic acids encoding the same. The invention further relates to vectors and cells comprising the nucleic acids and proteins of the invention as these are useful for, *inter alia*, the development of therapeutics.

Claims 1-86 are pending in the present application. Claims 9-15, 26, 28-36 and 38-86 have been withdrawn from further consideration as being drawn to non-elected inventions. Claims 1, 2, 16, 17, 19, 20-25, 27 and 37 have been amended and claims 3-8 and 18 have been canceled herein. As such, claims 1, 2, 16, 17, 19-25, 27 and 37 are under consideration following entry of the present Amendment.

Claims 1, 2, 16, 17, 19, 20-25, 27 and 37 have been amended in accordance with the election required in the Restriction Requirement dated June 21, 2004 (Paper No./Mail Date 20040616) to recite the sequences as set forth in SEQ ID NO:1 and SEQ ID NO:2. These amendments to the claims do not constitute new matter as SEQ ID Nos. 1 and 2 are disclosed in the as filed application.

Objection to claims 25, 27 and 37

The Examiner has objected claims 25, 27 and 37 because the Examiner is of the opinion that these claims encompass non-elected subject matter. Specifically, the Examiner asserts that these claims encompass among others, a polypeptide, a fusion protein and an antibody, and therefore do not specifically recite a polynucleotide and means of expression thereof as required by the Restriction Requirement mailed June 21, 2004 and Response to Restriction Requirement mailed July 2, 2004.

Applicants, while not necessarily agreeing with the Examiner's reasoning, but rather in a good faith effort to expedite prosecution of this application, have amended claims 25, 27 and 37 herein to delete reference to non-elected subject matter. No new matter has been introduced by way of these claim amendments.

Rejection of claims 22 and 23 pursuant to 35 U.S.C. § 101

Claims 22 and 23 stand rejected pursuant to 35 U.S.C. § 101 because the Examiner contends that the claimed invention encompasses a cell as it occurs in nature and

therefore is directed to non-statutory subject matter. Applicants respectfully disagree with the Examiner. Applicants point out that claims 22 and 23 are patentable because they relate to a mammalian cell that has been modified *in vitro*. Therefore, claims 22 and 23 fully comply with the standards set forth in 35 U.S.C. § 101 with respect to statutory subject matter.

Rejection of claim 37 pursuant to 35 U.S.C. §112, first paragraph

Claim 37 has been rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner contends that a pharmaceutical composition as recited in claim 37 implies a therapeutic use. However, the Examiner contends that the specification does not provide sufficient support for any biological effects using the compositions of the present invention, for example an antisense molecule as an antagonist to TRANCE. The Examiner also contends that claim 37 lacks enablement for the recitation of the phrase “pharmaceutical composition” which the Examiner contends that the phrase implicates an intended use of an antisense molecule for the treatment or administration into an animal. Specifically, the Examiner contends that there is not adequate guidance as to how TRANCE inhibition by using an antisense molecule could be used therapeutically. Applicants traverse the rejection under 35 U.S.C. § 112, first paragraph, enablement, for the following reasons.

It is well-settled that applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and “representative samples are not required by the statute and are not an end in themselves” (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the

specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Applicants respectfully submit that claim 37 relating to a pharmaceutical composition is supported by the specification as filed. As discussed elsewhere herein, enablement does not require a working example, and experimentation is allowed so long as it is not undue. Applicants contend that the specification fully supports the invention of claim 37, which pertains to the alleged intended use of a TRANCE antagonist for treatment or administration in an animal. Applicants submit, without limiting the invention in anyway, that the specification discloses beginning on line 15 of page 68 that a TRANCE antagonist pharmaceutical composition of the present invention comprises an anti-sense TRANCE nucleic acid. Further, beginning on line 13 of page 70, it is disclosed that a several immunological diseases are related to the over-expression of TRANCE, and thus a TRANCE antagonist that inhibits the expression of TRANCE provides a method of treating such diseases.

Example 4 in the specification discloses differential expression of TRANCE on various T cell subsets. For example, it was observed that resting CD8+ and CD4+ memory cells expressed high levels of TRANCE whereas resting naïve CD8+ and CD4+ T cells did not express TRANCE mRNA. However, upon CD3-stimulation, both subsets of T cells upregulated TRANCE expression. It was also observed that the expression of TRANCE on activated T cells attributed to the enhanced survival of dendritic cells and therefore contributing to an immune response.

In addition to the expression of TRANCE on T cells, the specification discloses that TRANCE was observed to be expressed on osteoblasts and that the expression of TRANCE on osteoblasts was found to be required for osteoclast differentiation. As such, the specification demonstrates that the expression of TRANCE, whether on T cells or osteoblasts, plays a role on eliciting a biological effect.

Applications contend that the specification as filed fully teaches the use of an anti-sense TRANCE nucleic acid molecule as a TRANCE antagonist pharmaceutical composition for the inhibition of TRANCE expression. Based on the disclosure that some cells express detectable levels of TRANCE and that the up-regulation of TRANCE expression

following a stimulation results in a biological effect, one skilled in the art would recognize that an anti-sense TRANCE nucleic acid molecule would be able to regulate the expression of TRANCE and therefore regulated a biological effect. In addition, Applicants further submit herewith the post-filing reference of Granchi et al. (2004, Int. J. Cancer 111:829-838) which demonstrates that the invention has been further reduced to practice by others whereby the same methods as those included in the application were utilized to arrive at the results predicted in the as-filed application. This reference provides evidence that the disclosure of the as-filed specification enables the claimed invention, and argues against the Examiner's assertion that claim 37 lacks enablement. This reference is not prior art to the present application, but rather represents post-filing reduction to practice of the present invention. The contents of this reference are more fully discussed below.

Granchi et al. (2004, Int. J. Cancer 111:829-838) demonstrates post-filing reduction to practice of the present invention. Granchi demonstrates treatment of neuroblastoma cells with biologic modifiers of RANKL (RANKL is a longer version of TRANCE) such as antisense oligonucleotides. Specifically, Granchi demonstrates that the treatment of an antisense oligonucleotide significantly reduced RANKL transcript levels and protein levels in SH-SY5Y cells. Therefore, the results of Granchi demonstrate that the specification as-filed is in fact enabled for the claimed invention because Granchi arrived at the results predicted in the as-filed specification and demonstrated further reduction to practice of the present invention by using the same methods as those disclosed in the application.

Thus, in view of the present legal standards regarding enablement as discussed elsewhere herein, claim 37 is amply enabled by the specification as filed under 35 U.S.C. §112, first paragraph. Applicants respectfully submit that the specification as filed amply supports these claims because the skilled artisan, when armed with the teachings disclosed in the specification, would have been able to use an anti-sense TRANCE nucleic acid molecule comprising at least one phosphodiester analog bond as a TRANCE antagonist pharmaceutical composition to inhibit or prevent the expression of TRANCE at both the RNA and protein level. Thus, Applicants respectfully request that the rejection of claim 37 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Rejection of claims 2, 3, 5-8 and 16-24 pursuant to 35 U.S.C. §112, second paragraph

Claims 2, 3, 5-8 and 16-24 stand rejected pursuant to 35 U.S.C. §112, second paragraph, as being indefinite. Claims 3, 5-8 have been canceled herein thereby rendering the rejection moot as to these claims and therefore the rejection of the cancelled claims is not addressed further herein.

The Examiner is of the opinion that claims 2 and 16-21 are indefinite because the claims encompass molecules identified by “standard hybridization conditions”. Applicants, while not necessarily agreeing with the Examiner’s reasoning, but rather in a good faith effort to expedite prosecution of this application, have amended claim 2 to delete this phrase.

With respect to claims 16-21, which depend from claim 1, Applicants have amended claim 1 to recite a sequence identifier. As such, claims 16-21 as amended herein does not encompass molecules identified by “standard hybridization conditions” because the terms degenerate variant and fragments have been deleted from claim 1.

Applicants respectfully submit that claims 2 and 16-21, as amended, are not vague or indefinite in anyway and that these amendments overcome the rejection of claims 2 and 16-21, under 35 U.S.C. §112, second paragraph.

In addition, the Examiner has rejected claims 22 and 23 for being indefinite for the recitation of “TRANCE” and for not describing TRANCE in terms of structural or functional features. Applicants have spelled out the acronym TRANCE the first time the term is recited in the claims, for example in claim 1. Further, Applicants have amended claim 22 to recite that the DNA sequence encodes a TRANCE polypeptide, wherein the amino acid sequence of said TRANCE polypeptide consists of the amino acid sequence as set forth in Figure 2 (SEQ ID NO:2). No new matter has been added by way of these amendments.

The Examiner has also rejected claims 24 as being indefinite for recitation of the terms “conservative variant”, “analog”, and “derivative”. Claim 24 has been amended to delete reference to these terms herein, thereby rendering this rejection moot.

Applicants respectfully submit that claims 2 and 16-24, as amended fully comply with the requirements set forth under 35 U.S.C. §112, second paragraph. Thus, Applicants respectfully request that this rejection be reconsidered and withdrawn as to these claims.

Rejection of claims 1-8 and 16-23 pursuant to 35 U.S.C. §102(a)

Claims 1-8 and 16-23 stand rejected pursuant to 35 U.S.C. §102(a), as being anticipated by Anderson et al. (1997, Nature 390:175-179). In the Examiner's view, Anderson teaches a sequence comprising SEQ ID NO:2 with a single mismatch and teaches the sequence of SEQ ID NO:4 with a single mismatch, and thereby encompassing sequences and variants thereof of the sequences of the present invention. As such, the Examiner contends that Anderson anticipates the present invention as recited in claims 1-8 and 16-23. Claims 3-8 and 18 have been canceled and therefore the rejection to these claims is moot.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added)). Therefore, Anderson et al., must describe each and every element of the claims in order to anticipate the claims under Section 102(a).

Applicants have amended claims 1 and 2, and dependent claims therefrom to recite SEQ ID NO:1 and SEQ ID NO:2, neither of which is taught by Anderson. Anderson teaches a 317 amino acid peptide sequence and the corresponding nucleic acid sequence therefrom. However, SEQ ID NO:2 of the present application is a sequence consisting a 245 amino acid peptide sequence and SEQ ID NO:1 is the corresponding nucleic acid sequence therefrom. Thus, the amendments to these claims overcome the rejection of claims 1-8 and 16-23 because Anderson does not teach each and every single element of claims 1 and 2 as amended and as required under 35 U.S.C. §102(a). Accordingly, Applicants respectfully request that the rejection of claims 1-8 and 16-23 pursuant to 35 U.S.C. §102(a), be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 102(e)

U.S. Patent No. 6,242,213

Claims 1-8, 16-25, 27 and 37 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Anderson (U.S. Patent No. 6,242,213; the '213 patent). Specifically, the Examiner opines the '213 patent anticipates the instant invention because it discloses sequences that are degenerate variants of SEQ ID NO:1 and SEQ ID NO:3 of the present application.

Applicants respectfully submit that the '213 patent does not anticipate claims 1-8 and 16-25, 27 and 37 under 35 U.S.C. § 102(e). Applicants have cancelled claims 3-8 and 18

thereby rendering the rejection moot as to these claims. In addition, claims 1 and 2 have been amended to recite SEQ ID NO: 1 and SEQ ID NO:2.

The '213 patent teaches a 317 amino acid peptide sequence and the corresponding nucleic acid sequence therefrom. However, SEQ ID NO:2 of the present application is a sequence consisting a 245 amino acid peptide sequence and SEQ ID NO:1 is the corresponding nucleic acid sequence therefrom. Thus, the '213d oes not disclose each and every element of amended claims, and therefore cannot anticipate the present invention. Accordingly, Applicants hereby respectfully request that the rejection under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Boyle (U.S. Patent No. 5,843,678)

Claims 4-8, 18-25, 27 and 37 have been rejected under 35 U.S.C. § 102(e), as being anticipated by Boyle (U.S. Patent No. 5,843,678). Specifically, the Examiner is of the opinion that Boyle anticipates the instant invention by the disclosure of a sequence that is “identical” to the sequence of SEQ ID NO:4. Applicants have canceled claims 3, 5-8 thereby rendering this rejection moot as to these claims. In addition claims 1 and 2, and dependent claims therefrom have been amended to delete reference to SEQ ID NO:4. As such, Applicants hereby respectfully request that the rejection of claims 4-8, 18-25, 27 and 37 under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Summary

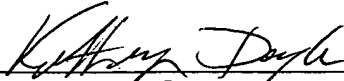
Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1, 2, 16, 17, 19-25, 27 and 37 are now in condition for allowance.


Respectfully submitted,

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December 30, 2004
(Date)

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Enclosure: Granchi et al. (2004, Int. J. Cancer 111:829-838)